

Gastrointestinal patch systems for oral drug delivery

Sarah L. Tao and Tejal A. Desai

Gastrointestinal patch systems with integrated multifunctions could surmount the challenges associated with conventional drug delivery. Several gastrointestinal patch systems provide bioadhesion, drug protection and unidirectional release. This combination of function could improve the overall oral bioavailability of large molecules that can currently be delivered only by injection, for example, epoetin- α and granulocyte-colony-stimulating factor, which are commonly used to treat chemotherapy-associated anemia and leukopenia, respectively. Furthermore, self-regulated release and cell-specific targeting provide additional 'smart' characteristics to this innovative therapeutic platform.

► Oral delivery is the preferred route for drug administration because it is more natural and less invasive than other traditional routes, such as intravenous and intramuscular injection. This, in turn, increases patient compliance and improves safety compared with other methods [1]. The pharmaceutical and biotechnology industries are continuously developing peptide, protein, biopolymer and macromolecular drugs for the treatment of a variety of diseases. However, many of these new drugs have poor bioavailability when administered orally and often fail to induce a clinical response. This is attributed to several factors, including: (i) a low mucosal permeability of a drug; (ii) the permeability of a drug being restricted to a particular region of the gastrointestinal (GI) tract; (iii) the low solubility of a compound, resulting in a low dissolution rate in mucosal fluids; and (iv) a drug being unstable in the GI environment, resulting in its degradation before absorption [2]. However, the major causes of the low oral bioavailability of macromolecular drugs are generally luminal enzymatic hydrolysis and low membrane permeability [3].

Several controlled release drug delivery strategies have been proposed to overcome these limitations. Protective coatings, such as lipids and polymers, as well as encapsulation technologies, such as microspheres and nanoparticles, have been used to protect peptides during transport through the acidic environment of the stomach and improve transport across the intestinal wall [4–8]. These types of systems, as well as layered dosages, have been proposed as a method for sustained release [9–11]. In an effort to increase the residence time of drug dosage forms in the GI tract, magnetic systems, gastric retentive units and systems incorporating mucoadhesive properties have been investigated [12–19]. In addition to non-specific mucoadhesion, cytoadhesive agents have been used to induce site-specific contact of peptides to the intestinal wall [2,20–22]. This allows for local delivery of peptides to sites in the GI tract, generating greater levels of absorption and stability. The use of permeation enhancers to augment uptake and transport through the intestinal wall, as well as protease inhibitors to protect peptides from enzymatic degradation, is also being explored [23–27].

Sarah L. Tao
Tejal A. Desai*
Departments of Physiology
and Bioengineering,
University of California,
San Francisco,
CA 94143, USA
and
Department of Biomedical
Engineering,
Boston University,
44 Cummington Street,
Boston,
MA 02215, USA
*e-mail: tdesai@bu.edu

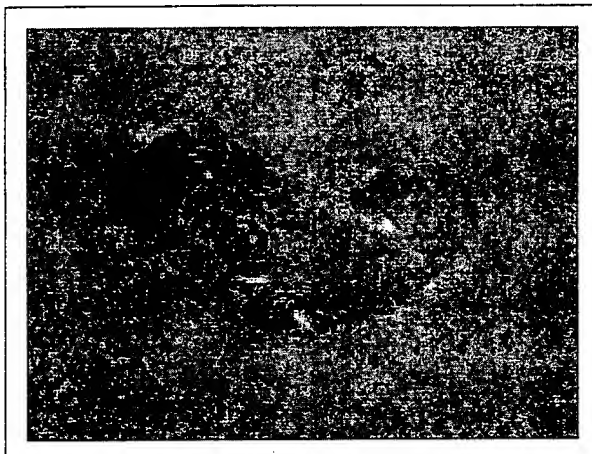


FIGURE 1
A capsule containing gastrointestinal mucoadhesive patch systems. Image kindly supplied by Kanji Takada.

Although all these approaches improve the oral bioavailability of large molecules, none of them offers a complete solution for adequate and safe oral administration.

One proposed approach for inducing greater levels of absorption and stability at the intestinal epithelium is the use of a multilayered patch system. Patch systems are more commonly used for the transdermal delivery of contraceptives and nicotine [28–30]. Patches comprise layers of thin, flexible membranes: an impermeable backing; a drug reservoir; a rate-controlling membrane; and an adhesive. When the patch is applied, the drug flows through the skin into the bloodstream at a rate regulated by the membrane that is preprogrammed to keep the drug at an effective level. More recently, buccal patch systems have been used to deliver drugs to the oral mucosa [31–34]. From a technological standpoint, these protective, rate-controlling and adhesive properties are also ideal for oral dosage forms intended for delivery to the intestinal mucosa. This review describes several GI patch systems that have three key attributes: (i) bioadhesive properties for retention of the dosage form; (ii) controlled drug-release; and (iii) unidirectional release towards the intestinal epithelium.

Gastrointestinal-mucoadhesive patch system

The first example of a patch system for oral drug delivery was the GI-mucoadhesive patch system (GI-MAPS) developed by Eaimtrakarn *et al.* [3,35]. This system consists of four layers: (i) a backing layer made of a water-insoluble polymer to protect protein drugs from enzymatic hydrolysis; (ii) a surface layer made of a polymer sensitive to intestinal pH; (iii) a drug-carrying middle layer; and (iv) an adhesive layer between the middle and surface layers to generate a high concentration gradient between the patch and intestinal enterocytes (Figure 1).

The backing layer of ethylcellulose was prepared by solvent evaporation. The middle layer, a cellulose membrane,

was loaded by wetting with a solution containing a model drug [e.g. fluorescein or granulocyte-colony-stimulating factor (G-CSF)] and was then dried and attached to the backing layer by thermal bonding. The pH-sensitive surface layer was prepared using one of three polymers – hydroxypropylmethylcellulose (HP-55), Eudragit® L100 or Eudragit® S100 (Röhm). The mucoadhesive layer, an aqueous solution of carboxyvinyl polymer [Carbopol® (Noveon)] and polyethylene glycol 400, was spread uniformly on the surface of the pH-sensitive layer and then attached to the middle layer. The four-layered film was cut into smaller pieces (0.5 mm in diameter for rat studies and 3.0 mm in diameter for dog studies) and treated with micro-pulverized stearic acid and magnesium silicate to cover the edges of the films to prevent patch agglutination.

Mucoadhesion and distribution of patch systems of varying pH-sensitivity was assessed in fasted male Wistar rats after intraduodenal administration to bypass the stomach environment [3]. Changing the pH-sensitive polymer used as the surface layer in GI-MAPS resulted in dissolution of the surface layer in different sections of the small intestine (corresponding to the pH threshold of the polymer), thereby exposing the mucoadhesive layer and controlling the time at which adhesion of the patch occurred. In this study, the pH of the small intestine ranged from ~6.6 in the duodenum and jejunum to 7.5 in the ileum. Patches containing a surface layer of HP-55, which has a dissolution threshold of pH 5.5, were retained >2 h in the duodenum before continuing transit. Those containing Eudragit® L100, which has a dissolution threshold of pH 6.0, were retained for ~2 h in the jejunum, whereas those containing Eudragit® S100, with a dissolution threshold of pH 6.8, were retained for ~2 h in the distal ileum.

To test targeting efficiency, GI-MAPS were prepared with each of the three different pH-sensitive surface layers loaded with 30 mg of fluorescein and administered to male beagle dogs. The plasma fluorescein concentration associated with HP-55 and Eudragit® L100 reached peak levels at ~2.3 and 3.3 h, respectively, after administration. However, the initial increase in plasma fluorescein levels associated with Eudragit® S100 system was delayed by ~2.3 h and peak levels were not reached until 5.0 h after administration. These data suggest that HP-55 and Eudragit® L100 systems dissolve in the upper and middle part of the small intestine, whereas the Eudragit® S100 system dissolves in the lower small intestine.

Furthermore, the pharmacological effects of GI-MAPS loaded with 125 µg of recombinant human G-CSF were evaluated by measuring circulating white blood cell counts. The pharmacological availability of G-CSF delivered by the patch system, compared with intravenous injection, was 5.5%, 23.0% and 6.0% for HP-55, Eudragit® L100 and Eudragit® S100 systems, respectively. It was thought that because the Eudragit® L100 GI-MAPS attached to the jejunum, where the hydrolytic enzyme activity is lower

than the duodenum and the effect of intestinal content is smaller than in the ileum, a higher pharmacological ability of G-CSF was associated with the Eudragit® L100 patch systems. This pharmacological availability was the highest value achieved compared with other drug delivery systems, including colonic delivery systems and an enteric effervescent system, where an organic acid and a non-ionic surfactant are used as additives to produce a synergistic absorption-enhancing effect [36,37].

Drug-in-adhesive patch

To increase the loading dose, Eaimtrakarn *et al.* [38,39] redesigned the intestinal patch with an increased loading space and without the adhesive layer. The reworked patch system consisted of three layers: (i) a backing layer of ethylcellulose; (ii) an enteric polymer membrane of HP-55; and (iii) a new drug-carrying layer, based on Carbopol®, loaded with 30 mg of fluorescein or fluorescein-dextran as a model drug. The three-layer preparation was heat sealed and cut into patches 3 mm in diameter. As a reference, the patches were compared with a compressed tablet of 30 mg of fluorescein or fluorescein-dextran mixed with microcrystalline cellulose. *In vitro* dissolution tests performed in pH 7.4 phosphate buffer at 37°C showed that 50% dissolution of fluorescein from the patch preparation was more than two times slower than from the tablet preparation.

Pharmacokinetic studies of the two test preparations, patches incorporating fluorescein or fluorescein-dextran, were carried out on adult beagle dogs at a dose of 30 mg/dog. For the patch and tablet preparations, no significant difference was observed in the maximum plasma concentration of fluorescein or in the time taken to reach maximum concentration. However, for the patch preparation, the mean residence time of fluorescein in plasma was ~1.5 times greater than the tablet preparations, whereas the mean residence time of fluorescein-dextran was 1.4 times greater than tablet preparation. This effect was ascribed to the increased residence time of the adhesive patches at the absorption site in the small intestine.

The three-layered oral patch preparation was also evaluated in human volunteers using caffeine as a model drug. This preparation consisted of an ethylcellulose backing

layer, a layer of Eudragit® L100 and a Carbopol®-based drug-carrying layer loaded with caffeine (50 mg). The three-layered preparation was heat-sealed, punched into patches 3 mm in diameter and administered in a batch of 120 by enteric encapsulation.

In vivo pharmacokinetic studies were carried out in fed and fasted human volunteers. Salivary caffeine excretion rate was used to evaluate the intestinal transit of the two test preparations. Under fasted conditions, the control preparation, which was an immediate release preparation, produced a mean maximum caffeine excretion rate of ~2 µg/min at 4 h, which subsequently rapidly decreased. Although the patch preparation showed a lower mean maximum caffeine excretion rate than the control (1.75 µg/min), it also showed a significantly higher mean residence time for caffeine (~6 h for the patch preparation versus 4 h for the control). Under fed conditions, the control and patch preparation had similar maximum excretion rates, with caffeine appearing 2–3 h later in saliva (for both preparations) compared with fasting conditions, indicating that the presence of food prolonged the gastric emptying time of the enteric capsules. The average data also indicated a longer mean residence time for the patch preparation than the control preparation. Overall, the human pharmacokinetic studies showed that the patch preparation produced a significantly longer mean residence time of caffeine in the small intestinal tract under fasting and fed conditions.

Microsphere patch

An alternative patch system, described by Shen *et al.* [40], similarly consists of three layers: (i) a mucoadhesive layer; (ii) a layer of drug-loaded microspheres partially immersed in the mucoadhesive layer; and (iii) an impermeable membrane encompassing the microspheres (Figure 2). To fabricate the patches, cross-linked bovine serum albumin (BSA) microspheres 10–30 µm in diameter were prepared and loaded with one of three model drugs [sulforhodamine B, phenol red or fluorescein isothiocyanate (FITC)-dextran]. The microspheres were spread uniformly and partially pressed into a 5 µm thick mucoadhesive layer made of Carbopol® and pectin, which was then covered with an ethylcellulose layer. After drying, the three-layered film was cut into smaller squares and circles.

In vitro release of sulforhodamine B from patches (4 mm in diameter) into phosphate buffered saline (PBS) was measured in a diffusion cell. It was found that 95% of the drug was released from the mucoadhesive side, which is significantly higher than from the backing side. Drug transport across the intestine from patches (~3 mm in diameter) was tested *in vitro* on explanted Sprague Dawley rat intestine sections. The intestinal sections were immersed and infused with PBS at a flow rate of 0.05 ml/min. The amount of drug transported across the intestinal wall was determined by measuring the concentration of model drugs in the receiver fluid. Control experiments were

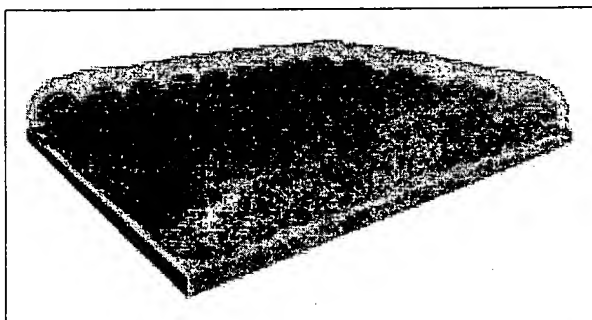


FIGURE 2
A microsphere patch design. Image kindly supplied by Samir Mitragotri.

performed by injecting the same total amount of model drug in solution into the intestinal lumen. A significant enhancement in transport across the intestinal wall was observed for all three model drugs: 30% of sulforhodamine B loaded in the patches was delivered across the intestine in 60 min compared with only 10% from solution; 45% of phenol red was delivered across the intestine from the patch system in 60 min compared with 10% from solution; and ~20% of dextran was delivered across the intestine from the patch system in 120 min compared with <10% from solution. The enhancement is attributed to the localization of the drug at the intestinal wall, thereby providing a high concentration gradient for delivery and the maintenance of unidirectional diffusion towards the wall.

Insulin patch for oral delivery

A bilayered intestinal patch was designed for the oral delivery of insulin [41]. These patches were fabricated using a mucoadhesive matrix of Carbopol®, pectin and sodium carboxymethylcellulose and loaded with bovine insulin (0.25–2.50 U/mg) as a model drug. This mixture was compressed under 0.5–4.0 tons using a hydraulic press and cut into disks with a diameter of 2–8 mm and a thickness of 400 μ m. Three sides of the patch were coated with a solution of ethylcellulose in acetone. The acetone was evaporated to obtain a 50 μ m thick ethylcellulose backing (Figure 3). The efficacy of the intestinal patch was evaluated in terms of insulin-induced hypoglycemia in rats, patch adhesion and insulin release.

In vitro release of insulin from 4 mm diameter patches was examined in a two-chamber diffusion cell in PBS. The studies showed that insulin was released from patches for ~4 h, with 99% being released from the mucoadhesive side. *In vivo* insulin delivery was conducted on male Sprague Dawley rats. Three to six patches that were 2 mm

in diameter and contained 0.25–1.20 U/patch were inserted in the jejunum. Alternatively, capsules containing patches with the same insulin dose, as well as 10 mg of sodium glycocholate, were also delivered by jejunal administration, rather than direct oral administration because of the large size of the capsules. Blood samples were collected from the tail vein or jugular vein and plasma insulin concentrations were measured. The intestinal patches led to reduction in blood glucose levels comparable to that resulting from subcutaneous injection of insulin. Hypoglycemia induced by insulin-loaded patches (2–10 fold higher than subcutaneous dose) fell between those induced by subcutaneous injection of 1 and 5 U/kg. Although the addition of sodium glycocholate enhanced insulin absorption, it was not essential because the intestinal patches induced significant hypoglycemia (>50%) without this additive. Delivery of insulin solution without sodium glycocholate and the solution prepared by patch dissolution in PBS induced no significant hypoglycemia. Hypoglycemic induction from patches delivered by capsules was slower than that induced by direct patch application; however, the minimum blood glucose level was identical to that of direct patch application (Figure 4b). This confirmed that the patches were able to exit the capsules, adhere to the mucosa and deliver insulin across the intestine. Furthermore, histological studies showed no changes in structure of the intestine between the use of intestinal patches and control preparations: there was no evidence of necrosis, specific inflammation or disruption of the epithelium.

Gated hydrogel patch

He *et al.* [42] were able to assemble a drug delivery system that provides controlled release (in addition to drug protection, simple mucoadhesion and unidirectional release) using a bilayered self-folding pH-sensitive hydrogel gate. The main device consisted of two parts – a poly(hydroxyl methacrylate) [p(HEMA)]-based drug reservoir with targeting function and a hydrogel gate. A hydrogel drug-entrapping matrix was prepared by free-radical photopolymerization at room temperature. Hydrogel disks 5 mm in diameter were cut, soaked in a solution containing the model drug acid orange 8 (AO8) or BSA and dried. The agent used to enhance mucoadhesion was a surfactant, Pluronic® F127 (BASF), a triblock polymer of poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide). The gate (5 mm in diameter and 60 μ m thick) was made from separate layers of p(HEMA) and poly(methacrylic acid-g-ethylene glycol) [p(MAA-g-EG)], partially cured atop one another. The drug reservoir, loaded hydrogel matrix and bilayered gate were then bonded together by photo-polymerization of the residual monomer from the partially cured bilayered gate.

Drug release from the device was controlled by the pH-dependent swelling properties of the bilayered gate (Figure 4). In pH 3.0 medium, p(MAA-g-EG) and p(HEMA) hydrogels showed similar swelling response, thus the gate remained

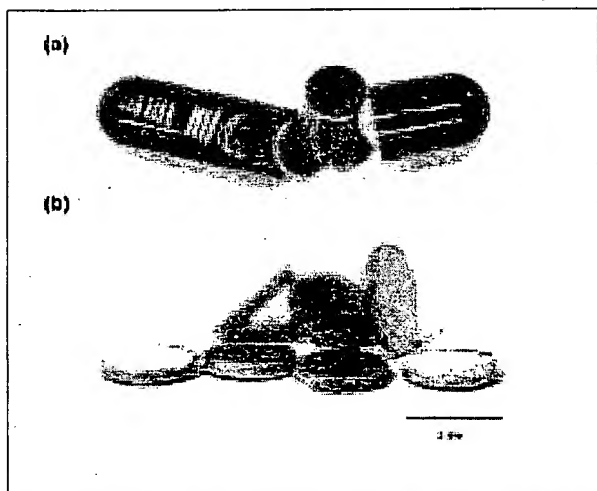


FIGURE 3
Intestinal patches for insulin delivery. (a) A capsule containing insulin patches. (b) A close up of the insulin patches. The backing membrane is stained with sulforhodamine B to aid visualization. Reproduced, with permission, from [41].

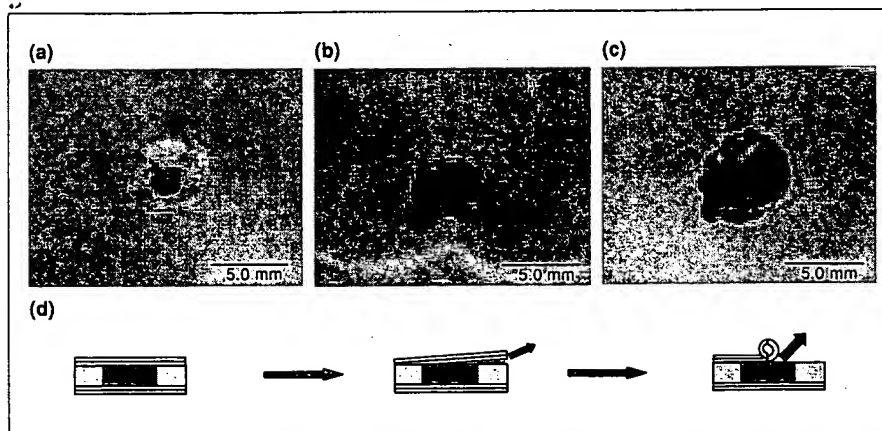


FIGURE 4 Acid orange 8 release from the assembled gated hydrogel patch at pH 7.3 and 25°C. The diameter of the device is 5.0 mm, the thickness of bilayered gate is 60 μm and the thickness of the drug reservoir is 1.0 mm. (a) Dry assembled device. (b) Release at 40 min. (c) Release at 80 min. (d) A schematic depicting AO8 release (Figure 4a–c) from an assembled device as the hydrogel gate opens. Reproduced, with permission, from [42].

closed and stable. No drug release was seen during a 2 h period. When the pH of the medium was increased to pH 7.3, swelling of the p(MAA-g-EG) increased significantly, whereas the swelling of the p(HEMA) layer remained constant. The increased swelling ratio caused the gate to fold outward until the bonding between the gate and reservoir broke, resulting in release of the drug. It took ~40 min to open the device gate, after which 90% of the drug was quickly released. Furthermore, pulsatile release can be achieved by altering pH. When the pH of the medium is returned to pH 3.0, the bilayered gate reverts to its closed state, resulting in a decreased release rate. Although the gate design has a limiting response time of minutes, the chemical structure of the hydrogel, gate thickness and the bilayer ratio can be altered to produce a response time of seconds.

Micropatches

The size of the particles can greatly affect the response generated in the body [43]. Although small particles of <5 μm have an increased adherence in the whole gut, they are more likely to induce a localized inflammatory response followed by phagocytosis by macrophages [44]. This leads to an increased risk of the carrier system being degraded after internalization, resulting in a loss of activity [44,45]. Particles of larger size are taken up less effectively by macrophages, therefore micropatches were fabricated that were large enough (diameter of 50–200 μm and thickness of 2–25 μm) to prevent endocytosis. However, the micropatches were designed to be small enough to travel between intestinal villi, thereby maximizing the large absorptive surface area the intestinal folds provide. The processes for fabricating micropatches in the three different substrates [silicon oxide, porous silicon and poly(methyl methacrylate) (PMMA)] have been developed based on standard microelectromechanical systems (MEMS) techniques, including photolithography, etching and thin film deposition.

Silicon oxide

Ahmed *et al.* [46,47] fabricated microdevices from a low temperature oxide (LTO) deposited by low-pressure chemical-vapor deposition onto silicon p-type wafers of <111> crystal orientation. The device geometry was defined by a series of photolithography and reactive ion etch (RIE) steps. Photolithography, the process by which a photosensitive polymer (photoresist) is exposed to ultraviolet light through a photomask, was used to pattern the device features. The features were then carved into the LTO by RIE using SF_6 and O_2 plasma (Figure 5a).

Poly(methyl methacrylate)

PMMA microdevices were fabricated on Radio Corporation of America-cleaned

silicon <111> p-type wafers, which were first spin-coated with multilayers of PMMA, followed by a layer of positive photoresist [49]. A series of photolithography and RIE steps was used to define the device geometry. After exposure and development of the photoresist, the unmasked area of PMMA was reactive ion etched using O_2 plasma (Figure 5b).

Porous silicon

Porous silicon microdevices were fabricated on a single-side polished silicon <100> p-type wafer coated with silicon nitride [48]. Photolithography was initially performed to define the area of intended porosity while protecting all other areas of the wafer. The backside of the wafer was then etched with SF_6 to strip the layer of silicon nitride. Exposed silicon nitride on the frontside of the wafer was etched with SF_6 and the remaining photoresist stripped. The patterned wafers were then anodized and electropolished in an ethanol-hydrofluoric acid solution [1:1 (v/v) for anodization; 4:1 (v/v) for electropolishing] in a custom built anodization tank. Porosification took place exclusively along the anodic side of the silicon wafers. Pore size and shape depend on the type of silicon used, the resistivity of the silicon, the current density and the concentration of hydrofluoric acid solution (Figure 5c).

Rather than depending on simple mucoadhesion, the micropatches were modified to include cytoadhesive cell-targeting capabilities. The basic synthesis for incorporating cytoadhesive properties into these microfabricated platforms had three major steps: (i) amine groups were formed on the device; (ii) avidin was coupled with conventional carbodiimide coupling reagents to form an avidin carboxylate that, in turn, was reacted with the amine groups of the substrate to form an avidin conjugate; and (iii) biotinylated lectins were attached to the surface using the strong interaction and affinity between avidin and biotin [46,50].

Microinjections were used to load the silicon oxide and PMMA micropatches with pico- to nano-liters of a polymeric solution. Water quickly evaporates from these reservoirs, leaving the drug contained in polymer, which acts as a timed-release plug. However, capillary action was exploited to load the polymeric solution into the porous silicon microdevices. Once the solution was taken into the pores, the porous silicon micropatches were dried by applying

vacuum pressure until any air trapped within the pores was released. By using a specific type of polymer, the time and rate of release of a drug from the reservoir could be predetermined; for example, a polymer with a known dissolution rate or a hydrogel that swells in response to a specific pH, solvent or temperature could be used. Different polymers with various dissolution rates could then be used in separate reservoirs to obtain controlled release of several compounds.

In vitro studies were performed using the Caco-2 cell line to measure the cytoadhesive properties of lectin-conjugated microdevices. The binding characteristics of microdevices modified with two types of lectin (tomato, known to agglutinate Caco-2 cells, and peanut, an unrelated lectin non-specific to Caco-2 cells) were observed as a function of time. Although both lectin conjugates produce a higher degree of binding than the pristine microdevices, a marked difference still remains between the peanut and tomato lectin conjugates (tomato lectin exhibited approximately twofold higher binding).

The Caco-2 model was also used to test drug transport through paracellular tight junctions, similar to those found in the intestinal lining. On microdevice application, the rate of permeation of a model drug, FITC-labeled insulin, through the monolayer was measured using fluorescence spectroscopy. Concurrent measurement of the total resistance across the membrane was also measured to determine the magnitude of the physiologic response of tight junction opening. The effect of transport by microdevice delivery was compared with that of a liquid formulation. It was found that drug transport efficiency increased when drug formulations were delivered from microdevices rather than liquid formulations. This efficiency increased tenfold with the use of a permeation enhancer. The dramatically increased flux caused by microdevice delivery is a result of a high concentration of permeation enhancer (sodium laurate) and FITC-insulin at tight junctions.

Conclusion

Over the past decade, several new patch systems have been developed to provide more effective oral drug delivery. These systems were designed to achieve the difficult task of performing multiple functions using a single platform, namely drug protection, unidirectional release and bioadhesion. Some of the technologies described here are already in evaluation for the delivery of large molecules, such as the drug-in-adhesive patch for delivery of G-CSF, erythropoietin and interferon- α , and the insulin patch for oral delivery of insulin. Others, such as the gated hydrogel patch, have the potential to produce complex pulsatile release patterns. This delivery method could mimic more naturally the way in which the body produces compounds, such as insulin and some hormones. The integration of microfabrication technology might enable the translation of some of the same functions associated with patch systems into devices on an even smaller scale. Although lower

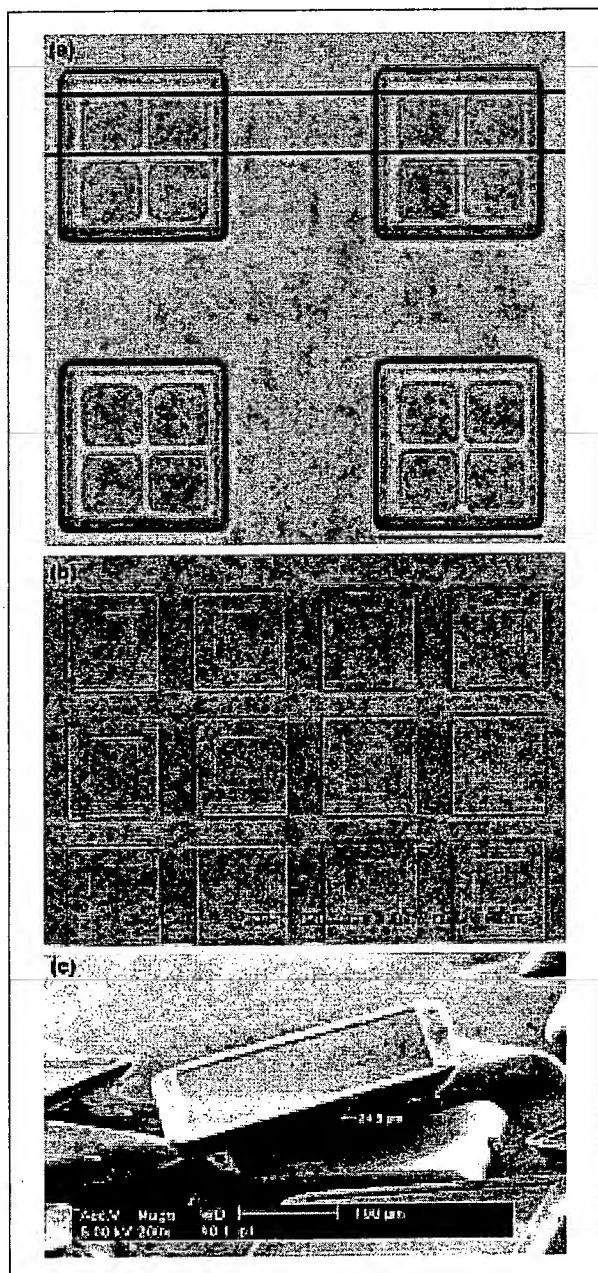


FIGURE 5

Polymer- and silicon-based micropatches. (a) Silicon dioxide microdevices with different 35 μm diameter reservoirs inside a 100 μm diameter body 2 μm thick. Bar represents 100 μm . (b) Scanning electron micrograph of PMMA microdevices with 80 μm diameter reservoirs in a 150 μm diameter body 5 μm thick. (c) Scanning electron micrograph of a porous silicon microdevice with a 200 μm diameter reservoir in a 250 μm diameter body 25 μm thick. Image kindly supplied by iMEDD.

amounts of drug can be held in an individual micropatch, a comparable drug dose could be achieved by increasing the number micropatches administered. Furthermore, because they are capable of traversing between intestinal undulations, micropatches maximize utilization of the absorptive intestinal surface area. As the scale decreases, these types of complex delivery systems could be delivered not only by ingestion (~1 mm), but also by injection into

tissue (<200 μm), inhalation (<100 μm) or even released into the systemic circulation (<10 μm) [51]. In the near future, integrated 'smart' devices capable of fully autonomous delivery and site-specific cell targeting will have a considerable impact on drug administration. As novel materials and technologies continue to emerge, the goal of manufacturing the ideal intelligent drug delivery device is rapidly being realized.

References

- Lavelle, E.C. (2001) Targeted delivery of drugs to the gastrointestinal tract. *Crit. Rev. Ther. Drug Carrier Syst.* 18, 341-386
- Ponchel, G. and Irache, J. (1998) Specific and non-specific bioadhesive particulate systems for oral delivery to the gastrointestinal tract. *Adv. Drug Deliv. Rev.* 34, 191-219
- Eaimtrakarn, S. et al. (2001) Retention and transit of intestinal mucoadhesive films in the rat small intestine. *Int. J. Pharm.* 224, 61-67
- Saffran, M. et al. (1990) Biodegradable azopolymer coating for oral delivery of peptide drugs. *Biochem. Soc. Trans.* 18, 752-754
- Iwanaga, K. et al. (1999) Application of surface-coated liposomes for oral delivery of peptide: effect of coating the liposome's surface on the GI transit of insulin. *J. Pharm. Sci.* 88, 248-252
- Jerry, N. et al. (2001) *In vivo* absorption studies of insulin from an oral delivery system. *Drug Deliv.* 8, 19-23
- Florence, A.T. and Hussain, N. (2001) Transcytosis of nanoparticle and dendrimer delivery systems: evolving vistas. *Adv. Drug Deliv. Rev.* 50, S69-S89
- McClean, S. et al. (1998) Binding and uptake of biodegradable poly-DL-lactide micro and nanoparticles in intestinal epithelia. *Eur. J. Pharm. Sci.* 6, 153-163
- Abdul, S. and Poddar, S.S. (2004) A flexible technology for modified release of drugs: multi layered tablets. *J. Control. Release* 97, 393-405
- Sinchaipanid, N. et al. (2004) Influences of layering on theophylline pellet characteristics. *Pharm. Dev. Technol.* 9, 163-170
- Rowe, C.W. et al. (2000) Multimechanism oral dosage forms fabricated by three dimensional printing. *J. Control. Release* 66, 11-17
- Groning, R. et al. (1996) Peroral controlled release dosage forms with internal magnets and extracorporeal magnetic guidance investigations into the renal elimination of riboflavin. *Eur. J. Pharm. Biopharm.* 42, 25-28
- Häfelj, U.O. (2004) Magnetically modulated therapeutic systems. *Int. J. Pharm.* 277, 19-24
- Dorkoosh, F.A. et al. (2004) Feasibility study on the retention of superporous hydrogel composite polymer in the intestinal tract of man using scintigraphy. *J. Control. Release* 99, 199-206
- Timmermans, J. and Moes, A.J. (1994) Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsule: new data for reconsidering the controversy. *J. Pharm. Sci.* 83, 18-24
- Sakkinen, M. et al. (2004) Gamma scintigraphic evaluation of the fate of microcrystalline chitosan granules in human stomach. *Eur. J. Pharm. Biopharm.* 57, 133-143
- Peppas, N.A. and Huang, Y. (2004) Nanoscale technology of mucoadhesive interactions. *Adv. Drug Deliv. Rev.* 56, 1675-1687
- Roldo, M. et al. (2004) Mucoadhesive thiolated chitosans as platforms for oral controlled drug delivery: synthesis and *in vitro* evaluation. *Eur. J. Pharm. Biopharm.* 57, 115-121
- Krauland, A.H. et al. (2004) Oral insulin delivery: the potential of thiolated chitosan-insulin tablets on non-diabetic rats. *J. Control. Release* 95, 547-555
- Arango, M.A. et al. (2000) Bioadhesive potential of gliadin nanoparticulate systems. *Eur. J. Pharm. Sci.* 11, 333-341
- Lehr, C.M. (2000) Lectin-mediated drug delivery: the second generation of bioadhesives. *J. Control. Release* 65, 19-29
- Nalsbett, B. and Woodley, J. (1995) The potential use of tomato lectin for oral drug delivery: 3. bioadhesion *in vivo*. *Int. J. Pharm.* 114, 227-236
- Fasano, A. and Uzzau, S. (1997) Modulation of intestinal tight junctions by *Zonula occludens* toxin permits enteral administration of insulin and other macromolecules in an animal model. *J. Clin. Invest.* 99, 1158-1164
- Guggi, D. and Bernkop-Schnurch, A. (2005) Improved paracellular uptake by the combination of different types of permeation enhancers. *Int. J. Pharm.* 288, 141-150
- Bernkop-Schnurch, A. et al. (2003) Permeation enhancing polymers in oral delivery of hydrophilic macromolecules: thiomers/GSH systems. *J. Control. Release* 93, 95-103
- Schwarz, U.I. et al. (2000) P-glycoprotein inhibitor erythromycin increases oral bioavailability of talinolol in humans. *Int. J. Clin. Pharmacol. Ther.* 38, 161-167
- Morishita, M. et al. (1993) Site-dependent effect of aprotinin, sodium caprate, Na₂EDTA and sodium glycocholate on intestinal absorption of insulin. *Biol. Pharm. Bull.* 16, 68-72
- Davaran, S. et al. (2005) Development of a novel prolonged-release nicotine transdermal patch. *Pharmacol. Res.* 51, 233-237
- Burkman, R.T. (2004) The transdermal contraceptive system. *Am. J. Obstet. Gynecol.* 190, S49-S53
- Thomas, B.J. and Finnin, B.C. (2004) The transdermal revolution. *Drug Discov. Today* 9, 697-703
- Nagai, T. and Machida, Y. (1993) Buccal delivery systems using hydrogels. *Adv. Drug Deliv. Rev.* 11, 179-191
- Anders, R. and Merkle, H.P. (1989) Evaluation of laminated muco-adhesive patches for buccal drug delivery. *Int. J. Pharm.* 49, 231-240
- Merkle, H.P. and Wolany, G.J.M. (1996) Mucoadhesive patches for buccal peptide administration. In *Buccal and Nasal Administration as an Alternative to Parenteral Administration*. pp. 110-124, Editions de Sante Paris
- Remunan-Lopez, C. et al. (1998) Design and evaluation of chitosan/ethylcellulose mucoadhesive bilayered devices for buccal drug delivery. *J. Control. Release* 55, 143-152
- Eaimtrakarn, S. et al. (2002) Gastrointestinal mucoadhesive patch system (GI-MAPS) for oral administration of G-CSF, a model protein. *Biomaterials* 23, 145-152
- Takada, K. et al. (1994) Pharmacological activity of tablets containing recombinant human granulocyte colony-stimulating factor (rhG-CSF) in rats. *Int. J. Pharm.* 101, 89-96
- Takaya, T. et al. (1995) Development of a colon delivery tablet and the pharmacological activity of recombinant human granulocyte colony-stimulating factor in beagle dogs. *J. Pharm. Pharmacol.* 47, 474-478
- Eaimtrakarn, S. et al. (2003) Possibility of a patch system as a new oral delivery system. *Int. J. Pharm.* 250, 111-117
- Eaimtrakarn, S. et al. (2002) Evaluation of gastrointestinal transit characteristics of oral patch preparation using caffeine as a model drug in human volunteers. *Drug Metab. Pharmacokinet.* 17, 284-291
- Shen, Z. and Mitragotri, S. (2002) Intestinal patches for oral drug delivery. *Pharm. Res.* 19, 391-395
- Whitehead, K. et al. (2004) Oral delivery of macromolecules using intestinal patches: application for insulin delivery. *J. Control. Release* 98, 37-45
- He, H. et al. (2004) Design of a novel hydrogel-based intelligent system for controlled drug release. *J. Control. Release* 95, 391-402
- Tomazic-Jezic, V.J. et al. (2001) Significance of the type and the size of biomaterial particles on phagocytosis and tissue distribution. *J. Biomed. Mater. Res.* 55, 523-529
- Tabata, Y. et al. (1996) Size effect on systemic and mucosal immune responses induced by oral administration of biodegradable microspheres. *Vaccine* 14, 1677-1685
- Mody, R. et al. (1995) Use of lectins as diagnostic and therapeutic tools for cancer. *J. Pharmacol. Toxicol. Methods* 33, 1-10
- Ahmed, A. et al. (2002) Bioadhesive microdevices with multiple reservoirs: a new platform for oral drug delivery. *J. Control. Release* 81, 291-306
- Ahmed, A. et al. (2001) Bioadhesive microdevices for oral drug delivery: a feasibility study. *Biomed. Microdevices* 3, 89-96
- Tao, S.L. et al. (2003) Bioadhesive poly(methyl methacrylate) microdevices for controlled drug delivery. *J. Control. Release* 88, 215-228
- Foraker, A.B. et al. (2003) Microfabricated porous silicon particles enhance paracellular delivery of insulin across intestinal Caco-2 cell monolayers. *Pharm. Res.* 20, 110-116
- Tao, S.L. et al. (2003) Synthesis of cytoadhesive poly(methylmethacrylate) for applications in targeted drug delivery. *J. Biomed. Mater. Res. A* 67, 369-375
- LaVan, D.A. et al. (2003) Small-scale systems for *in vivo* drug delivery. *Nat. Biotechnol.* 21, 1184-1191